REMARKS

This paper is responsive to the Office Action dated February 25, 2004, which is the first action on the merits of the application.

Claims 1, 11-17, 30-32, 35, and 37-52 were previously pending; claims 1, 11-15, 17, 30-32, and 35 were withdrawn from consideration. Claims 37-52 have been included in the group under examination, for which applicant is grateful.

Upon entry of this paper, claims 2-15 and 17-36 are cancelled, certain claims are amended, and claims 53-62 are added. The new claims also fall within the elected group. Accordingly, claims 1, 16, and 37-62 are pending, and all but claim 1 are under examination.

Applicant is grateful to the Examiner for considering all the information provided in Information Disclosure Statements previously filed in this application.

Reconsideration and allowance of the application is respectfully requested.

Amendments:

Entry of the amendments to the specification does not introduce new matter into the disclosure. Additional wording present in paragraph [0100] is taken from USSN 60/213,739, page 21, lines 10-13. This application claims the priority benefit of USSN 60/213,739, and incorporates it by reference on page 1, lines 13-18 of the application as filed.

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the use of extracellular matrix in the feeder-free culture system of the invention can be found in several places in the disclosure, such as page 15, lines 15-27, Example 2 (page 40 ff.), and Figure 3. Equivalents of extracellular matrix are also covered. New claims 53-62 are supported by claims 37, 46, 47, 48, 52, 43, 44, 46, 48, and 52 as previously presented.

Priority

Paragraph [0001] has been amended to address the relationship between the priority applications, as requested in the Office Action.

PCT/US01/01030 (designating the U.S.) and USSN 09/688,031 need not be referred to in the Declaration under 37 CFR § 1.63, since neither constitutes a foreign application for the purposes of 35 USC § 119.

Claim objections

Claim 16 has been amended so as not to depend from a non-elected claim, as requested.

Claim 40 further limits claim 37 from which it depends, by requiring the cells to be differentiated. Claim 37 only provides the "option" (step b) of causing the pPS cells to differentiate. As an alternative, the cells may be left in undifferentiated form (claim 39). Claim 37 has been rewritten in independent form to avoid any confusion on this issue.

Double Patenting

Certain claims in this application stand provisionally rejected for double patenting, with respect to certain claims of pending applications USSN 10/157,288; 09/888,309; 10/087,473; 10/087,142; 10/313,739; and 10/189,276.

The pending claims in USSN 09/888,309 (Geron docket 090/002) pertain to the making and use of neural lineage cells using TGF-β Superfamily Antagonists such as noggin. The use of noggin is not taught or suggested in the present application. Applicant respectfully submits that the claimed inventions in the two applications are patentably distinct.

The prosecution of the present application is further advanced than USSN 10/157,288 (Geron docket 094/011); USSN 10/087,473 (Geron docket 090/003); USSN 10/313,739 (Geron docket 132/002); and USSN 10/189,276 (Geron docket 098/003), for which applicant has not yet received a first Office Action on the merits. In the normal course of things, applicant expects the invention claimed in the present application to be patented before USSN 10/157,288; 10/087,473; 10/313,739; and 10/189,276.

Applicant undertakes to address the double patenting issue appropriately upon determination that the claims in the present application and in USSN 10/087,142 (Geron docket 093/005p) are otherwise patentable.

Rejections under 35 USC § 112 ¶ 1:

The claims previously under examination stand rejected under the enablement requirement of § 112 ¶ 1. The Office Action indicates that the specification is enabling for methods of screening using pPS cells growing in a culture essentially free of feeder cells on an extracellular matrix in a fibroblast conditioned medium, but not in other media. The Office Action cites an article by Lim et al (Proteomics 2:1187, 2002) as indicating that the feeder cells provide complex interaction with the

embryonic stem cells comprising both membrane-bound and secreted factors that have not been identified.

Applicant is grateful for acknowledgement that the specification is enabled to the extent indicated in the Office Action.

In fact, the Lim article does not undermine the patentability of the invention claimed here; it demonstrates its inventive nature. Lim assumes that all of the complex interactions provided by feeder cells are required for hES cells to be grown. The article indicates the use of a feeder cell of some sort and serum-containing medium will (inevitably) be required.

In contrast, the present disclosure shows that effects obtained by direct contact with the feeder cells can be replaced with contact with extracellular matrix components — and furthermore, that a relatively uncomplicated nutrient medium (not necessarily containing serum) can provide all the other support required for undifferentiated cell growth. The feeder-free culture system of the present invention is elegant in its simplicity. It is patentable not only because of its effectiveness, as exemplified in the specification, but also because it *defies the conventional teaching* in the ES cell art, as illustrated in the teachings of Thomson et al. (Proc. Natl. Acad. Sci. USA 92:7844, 1995) and the cited Lim reference.

The following arguments parallel those made in copending applications USSN 09/859,291 and 09/859,291, in which similar issues were raised.

By making these rejections under § 112 ¶ 1, the Office seeks to limit applicant's coverage to conditions that were exemplified in the working examples. But the details of growth conditions selected for the working examples, such as the medium used, are not critical features of the new feeder-free culture method described and enabled by the application.

Federal Circuit case law clearly establishes that a patent applicant is not required to limit coverage to the working examples. Broader coverage is available under § 112 ¶ 1, providing there is no prior art that encroaches on the claimed scope outside the working examples.

For example, *In re Peters*, 221 USPQ 952 (Fed. Cir. 1983) and *In re Rasmussen*, 211 USPQ 323 (Cust. & Pat. App. 1981) both held that applicants are entitled to eliminate a non-critical limitation from the claims in a reexamination application, *even though the Patent Office demonstrated in each case that the specification had no working example that omitted the limitation at issue.* Similarly, the PTO was found to err when it rejected a claim to an analog of human γ-interferon having only one particular alteration, when the specification taught how to make an analog that had the

same alteration in combination with another alteration. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996).

The specification of the present application clearly indicates that the aspects of the culture system referred to in the current Office Action are not considered critical to the invention. In the section of the Detailed Description dealing with the culture of pPS cells in the absence of feeders, key elements of the medium are indicated on page 16, lines 8-11.

> pPS cells plated in the absence of fresh feeder cells benefit from being cultured in a nutrient medium. The medium will generally contain the usual components to enhance cell survival, including isotonic buffer, essential minerals, and either serum or a serum replacement of some kind.

The description goes on to highlight the use of conditioned medium as a possible nutrient medium to be used in the feeder-free environment. At the time the application was filed, conditioned medium was a preferred embodiment of the invention. For this reason, the manufacture and use of conditioned medium was elaborated, in a sprit of full disclosure and compliance with the best mode requirements of § 112 ¶ 1.

In addition, some of the cell lines used to condition the medium represent an embodiment of the invention for which coverage is being sought in a related application. Such cell lines include any human cell including but not limited to those obtained by differentiating hES cells that have appropriate characteristics to condition medium, which can be identified according to the testing procedure described on page 18, line 23 to page 19, line 10. Suitable cells may have features that are characteristic of fibroblasts, or other cell types such as *mesenchymal cells* (page 17, lines 22-25).

However, none of these aspects of the culture environment exemplified in the specification are meant to limit the feeder-free system of the invention (as embodied in the present claims) to the particular culture conditions used in the working examples. By way of this amendment, wording has been incorporated into the specification from priority application USSN 60/213,739. This wording confirms what would already be apparent to the skilled reader — that the feeder-free system can be practiced not only by conditioning the nutrient medium by preculturing with feeder cells, but by synthetically assembling an effective nutrient medium by adding the growth factors directly to fresh medium.

Now that applicant has demonstrated that human ES cells can be established and maintained in a feeder-free environment, working alternatives can be identified and used by the skilled reader. By

employing the culture test system and the marker assessment protocol provided in the specification (e.g., Examples 1-3), synthetically assembled media can be used and assessed to identify effective combinations of culture environment components. Now that applicant has disclosed the feeder-free system to the art by the filing and publication of this patent application, it would be unfair to limit applicant to culture conditions exemplified in the working examples.

Besides the results shown in the working examples of this patent disclosure, the scientists at Geron have also demonstrated that human ES cells readily grow in fresh medium with added growth factors. X-VIVO™ 10 and QBSF™-60 (two commercially available formulations) have been tested and found useful as suitable base nutrient medium. Extracellular matrix replaces the signaling provided by feeder cells in feeder-supported culture, supplemented with soluble factors such as basic FGF (page 16, lines 26-32 of the specification). The synthetic medium supports expansion of human ES cells in an undifferentiated form for prolonged culture, as demonstrated by retention of markers characteristic of the undifferentiated phenotype, and by sustained ability to differentiate into tissue types representing all three germ layers.

To expedite prosecution of the application, the claims have now been amended to incorporate the limitations of claim 38 into base claim 16, 37, and 53: Specifically, the culture environment contains an extracellular matrix or its equivalent. Applicant respectfully submits that the base claims need not also recite the use of conditioned medium, since this is a preferred embodiment, and not a critical limitation.

Withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 112 ¶ 2:

Claims 37 and 39 stated rejected as confusing or unclear for indicating that the undifferentiated pPS cells are optionally caused to differentiate.

The use of the term "optionally" is a suitable alternative format that can comply with § 112 ¶ 2, providing that the alternatives have no ambiguity. See MPEP § 2173.05(h)(III), citing *Ex parte Cordova,* 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989). In claim 37, the alternatives are clear: either the pPS cells can be left in the undifferentiated state (claim 39); or caused or permitted to differentiate (e.g., claims 40-44). The specification and the claims as previously presented clearly contemplate screening techniques using both undifferentiated and differentiated cells.

Claim 37 has been rewritten in independent form to clear up any confusion in this respect. Applicant is grateful to the Examiner for providing an opportunity to improve the claim language in this respect.

Request for Interview

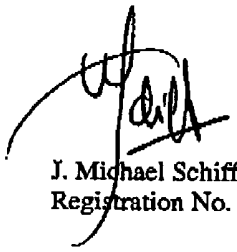
Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested. In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

Fees Due

No fee is believed due for consideration of this paper: 36 claims and 10 independent claims have previously been paid for.

Nevertheless, should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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May 24, 2004

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Last page of this transmission